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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/622,776	08/23/2000	John Burczak	DEX-0079	2610

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EXAMINER	
UNGAR, SUSAN NMN	
ART UNIT	PAPER NUMBER
1642	6

DATE MAILED: 05/02/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/622,776	Burczak et al
Examiner	**Art Unit**
Ungar	1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Mar 4, 2002* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-3, 5-8, and 10-15* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-3, 5-8, and 10-15* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
18) ☐ Interview Summary (PTO-413) Paper No(s). _____
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

1. The Amendment filed March 4, 2002 (Paper No. 5) in response to the Office Action of October 2, 2002 (Paper No. 3) is acknowledged and has been entered. Previously pending claims 4 and 9 have been canceled, claims 1, 6, 10, 13 have been amended. Claims 1-3, 5-8, 10-15 are currently being examined.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention."

4. Claims 1-3, 5-8 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Since it appears that the enzyme level cut-off recited is meant to be a level at or above 4.5 ng/ml, rather than at or below 4.5 ng/ml, it will be assumed for examination purposes that the enzyme level cut-off is at or above 4.5 ng/ml.

The claims are drawn to a method of monitoring cancer in a patient for the onset of metastasis comprising detecting levels of PLA2 in a sample of a bodily fluid wherein levels at or above 4.5 ng/ml is indicative of the onset of metastasis of

cancer (claims 1-3 and 5), a method of diagnosing a metastatic cancer in a patient comprising detecting levels of PLA2 in a sample of bodily fluid wherein levels at or above 4.5 ng/ml is indicative of metastatic cancer (claims 6-8).

The specification teaches that this invention relates to the use of PLA2 as a metastatic marker for monitoring cancers which have not metastasized for the onset of metastasis and for diagnosing metastatis (p. 1, lines 12-25). It has been found that PLA2 levels are significantly higher in human patients with metastatic cancer as compared to cancer which has not yet metastasized (p. 9, lines 3-5). This is seen in prostate cancer, breast cancer, colorectal cancer, testicular cancer and ovarian cancer. A positive result indicating that the cancer in the patient being treated or monitored has metastasized is one in which bodily fluid levels of the cancer marker PLA2 are elevated above an established enzyme immunoasay cut-off of 4.5 ng/ml. Table 1 shows the percent of individuals identified as positive with an EIA cutoff of 4.5 ng/ml in normal human controls, in patients having non-malignant disease, as well as four stages of prostate CA.. It is noted that in the Stage A patients, wherein the lesion is confined to the prostate, 7.1% of those tested, tested positive. In Stage B patients with locally metastasized prostate cancer 7.3% of those assayed tested positive. In Stage C with widely metastasized prostate cancer 11.8% of those assayed tested positive. In Stage D (not defined metastatically by the specification) 81.0 percent of those assayed tested positive. The specification teaches that PLA2 increases significantly in patients with Stage D prostate cancer as compared to other stages of cancer, accordingly, the claimed invention provides a useful means for diagnosing metastatic cancer and/or monitoring the onset of metastasis in patients

with prostate cancer which has not as yet metastasized (para bridging pages 13 and 14, prostate cancer staging recited on page 7, lines 14-27). Table 2 shows the percentage of individuals identified as positive based upon measurement of PLA2 in serum by an ELISA with an EIA cut-off of 4.5 ng/ml in patients having breast, colorectal, ovarian or testicular cancer wherein no normal patients appear to have been assayed, wherein 25% of the four nonmetastasized breast tumors patients, 33% of the three nonmetastasized colorectal patients, 50% of the six testicular patients and 0.0% of the single ovarian tumor patient tested positive. Further, the specification teaches that the percent of individuals positive for PLA2 decreases in patients with breast, ovarian or testicular cancer that are in remission or stabilized. One cannot extrapolate the teaching of the specification to the enablement of the claims because it is well known in the art that serum PLA2 levels above 4.5 ng/ml are commonly found in a plethora of patients, in various stages of progression (that is metastatic state) with at least 9 different types of cancer. For example, Yamashita et al (Clinica Chimica Acta 1994, 228:91-99) of record specifically teaches that the serum of patients with lung cancer, breast cancer, esophageal cancer, gastric cancer, colorectal cancer, liver cancer, bile duct cancer and pancreatic cancer all presented with PLA2 levels above 4.5 ng/ml (see Figure 1, page 94) and that the patients tested included stages T1-T4, N0-N1, M0-M1 and stages I-IV (see abstract), all of whom had serum PLA2 levels above 4.5 ng/ml (see Figure 1, page 94) and US Patent No. 5,747,264, of record, specifically teach that the serum of patients with prostate cancer present with PLA2 levels above 4.5 ng/ml. Although the specification teaches that, in some cases, high percentages of a general population

of cancer patients with known cancer stages present with PLA2 levels above 4.5 ng/ml, the specification does not teach how to extrapolate that information to the individual cancer patient so that one could either monitor for or detect metastatic disease. It is noted that US Patent No. 5,747,264 specifically teaches that normal healthy men without prostate disease have a serum level of 4.8 ng/ml (col 9, lines 48-51), thus the claimed method would identify every single subject tested in the referenced patent, whether normal or malignant, as having metastatic prostate cancer and would diagnose every single subject tested as having the onset of metastasis. Further, it is clear from the information in the specification, for example in prostate cancer patients, that even on the basis of a general population it is not possible to predict whether the percent of patients of that population has non-metastatic compared to metastatic cancer since the numbers demonstrate (and the specification clearly recognizes) that the percent population is the same for nonmetastatic as well as metastatic stages B and C. Further, although there appears to be a higher percentage of the populations of breast, colorectal and testicular cancer patients with progressive disease that have PLA2 levels above 4.5 ng/ml, the information cannot be fully evaluated because unlike the information presented for prostate cancer wherein the percent population information for the various stages of cancer were presented, all stages of the populations of breast, colorectal and testicular cancer patients appear to be lumped together. Thus it cannot be determined, even for the populations whether or not there is a difference, for example between non-metastasized tumors and those that are locally or even widely metastasized. Finally, it is clear that a substantial number of the nonmetastasized

patients tested (Table 2) also present with a positive score (it is noted that the result reported for ovarian cancer patients can not be evaluated given the single non-metastasized patient presented as a control). The specification teaches a statistical analysis of cancer populations that demonstrates that, in some cancer types and stages, a higher percentage of the population presents elevated levels of PLA2 in serum. The specification does not teach how to distinguish between the individual patients who have metastasized tumors and those who do not, based on PLA2 serum levels. The teaching in the specification and the exemplified data are not commensurate in scope with the claimed invention and given the information known in the art, no one of skill in the art would believe that it is more likely than not that metastatic cancer could be distinguished from nonmetastasized cancer or the onset of metastasis by detecting levels of PLA2 above 4.5 ng/ml as claimed.

As drawn specifically to monitoring the onset of metastasis, Frandsen et al (Fibrinolysis, 1992, 6, Suppl 4:71-76) specifically teaches that the processes of invasion and metastasis are basically divided into three main parts, (1) dissolution of the extracellular matrix, (2) cancer cell migration, (3) attachment either by cell-to-cell or cell-to-substrate interaction (p. 71, col 1). The specification does not define the meaning of "onset of metastasis". It is clear that the art recognized onset of metastasis as the dissolution of the extracelluar matrix. It cannot be predicted, nor would it be expected, from the information either in the specification or in the art that the dissolution of the extracellular matrix or even more advanced levels of metastasis such as cancer cell migration or the attachment of cells would result in an alteration of the level of PLA2. Further, given that the specification does not teach

how to distinguish between metastatic cancers and nonmetastatic cancers in an individual, it could not be predicted, nor would it be expected that it would be possible to monitor for the onset of metastasis as claimed. Further although the specification teaches that the number of patients with PLA2 elevated about 4.5 ng/ml increases significantly in patient populations with Stage D prostate cancer as compared to other stages of prostate cancer, and the specification teaches that the claimed invention provides a useful means for diagnosing metastatic cancer and/or monitoring the onset of metastasis in patients with prostate cancer which has not as yet metastasized (para bridging pages 13 and 14), the data in the specification, that can be fully evaluated, makes it clear that even looking at the population as a whole, it is not possible to monitor the onset of metastasis because there was no difference reported in percent population between nonmetastasized and widely metastasized, Stage C cancer patients. In view of the above, one of skill in he art would be forced into undue experimentation to practice the claimed invention.

5. Claims 1-3, 5-8 and 13-15 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Since it appears that the enzyme level cut-off recited is meant to be a level at or above 4.5 ng/ml, rather than at or below 4.5 ng/ml, it will be assumed for examination purposes that the enzyme level cut-off is at or above 4.5 ng/ml.

The claims are drawn to a method of monitoring cancer in a patient for the onset of metastasis, a method of diagnosing metastatic cancer and a method of

monitoring progression, remission, response to therapy and stabilization of prostate, breast, ovarian or testicular cancer, all comprising measuring PLA2 levels with an enzyme level cut-off of 4.5 ng/ml. The specification teaches that a positive result indicating that the cancer in the patient being treated or monitored has metastasized is one in which bodily fluid levels of the cancer marker PLA2 are elevated above an established enzyme immunoasay cut-off of 4.5 ng/ml (p. 12) and that the cut-off point of 4.5 ng/ml is the one used to monitor progression, remission, response to therapy and stabilization of prostate, breast, ovarian or testicular cancer (see claim 13). One cannot extrapolate the teaching of the specification to the enablement of the claims because the cut-off level claimed appears to be arbitrary chosen based on unreported assays and, as exemplified by US Patent No. 5,747,264, of record, and Yamashita (Clin. Chim. Acta), of record, it would be expected that the same or similar assays, in the hands of other research groups, would find different values for what would be expected to be normal control levels of PLA2 in serum. Yamashita teaches that the average stomach cancer patient has 3.7 ng/ml PLA2 in serum (see Figure 1, p. 94). Given this finding, not a single patient with stomach cancer would be diagnosed with cancer, much less metastatic cancer or even the onset of cancer. US Patent No. 5,747,264 specifically teaches serum levels of 4.85 ng/ml for normal healthy men without prostate disease and 5.31 ng/ml for normal healthy women and that the combined level of PLA2 in normal healthy men and women is 5.11 ng/ml. Thus, it would be expected for cancers in both men and women, that is for prostate, ovarian, testicular, breast cancer patients, every single subject tested would test positive for onset of metastasis, diagnosis of metastatic cancer and no one of

ordinary skill in the art would believe that it would be more likely than not that the claimed monitoring of progression, remission, response to therapy and stabilization of prostate, breast, ovarian or testicular cancer in the positively identified patients could be done with a reasonable expectation of success. In view of the above, one of skill in the art would be forced into undue experimentation to practice the claimed invention.

6. Claims 1-3, 5-8 and 10-15 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-3 and 5 are indefinite because in the preamble claim 1 recites the phrase "has not metastasized" and the body of the claim recites "having a cancer that is not known to have metastasized". The two statements are contradictory. The rejection can be obviated, for example, by amending the preamble to recite "which is not known to have metastasized.

Claims 1-3, 5-8, 13-15 are indefinite because claim 1 recites in section © "detecting levels of PLA2 with an enzyme level cut-off of 4.5 ng/ml". The claims are confusing because it is unclear whether Applicant is claiming the detection of PLA2 only up to a level of 4.5 ng/ml or whether Applicant is claiming detecting levels of PLA2 at or above an enzyme level of 4.5 ng/ml.

Claim 10-12 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete because claim 10 omits an essential step, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted step is comparing the levels to some sort of control to determine whether or not the levels are elevated.

Claims 13-15 are indefinite because claim 13 recites the phrase "enzyme level cut-off of 4.5" without any reference to any type of concentration. The rejection can be obviated by amending claim 13, for example to recite ng/ml.

Claim Rejections - 35 USC § 103

7. Claims 6-8 are rejected under 35 USC 103 as being unpatentable over US Patent No.5,747,264, of record in view of Yamashita et al (Clin. Chim. Acta), of record

The claims are drawn to a method of diagnosing ovarian or testicular cancer in a patient comprising obtaining a sample of biological fluid from a patient and detecting levels of PLA2 in the sample wherein elevated levels of PLA2 in the sample are indicative of ovarian or testicular cancer, wherein the fluid is serum, wherein the assay is ELISA.

US Patent No. 5,747,264 teaches as previously set forth, that is it teaches a method for diagnosis of cancer (see abstract) by detecting levels of PLA2 in bodily fluids wherein overexpression of PLA2 in bodily fluids compared to normal control bodily fluids may be used to detect the presence of cancers (col 2, lines 39-50) and specifically exemplifies the assay by ELISA in serum (cols 9-10) and specifically claims the method for detection of a carcinoma, prostate cancer. US Patent No. 5,757,264 teaches as set forth above but does not specifically teach a method of diagnosing ovarian or testicular cancer, at least a subset of which are carcinomas.

Yamashita et al teach that serum samples of patients, with lung cancer, breast cancer, esophageal cancer, gastric cancer, colorectal cancer, liver cancer, bile duct cancer, pancreatic cancer were tested for overexpression of PLA2. Instances of

overexpression of PLA2 compared to normal control in serum were found in every single one of the eight cancer types tested (See Figure 1, p. 94). It is noted that, all of the cancer types tested are notoriously well known to be either carcinomas or include a subset of carcinomas within the genus.

It would have been *prima facie* obvious to one of ordinary skill in the art, and one would have been motivated, at the time the invention was made to modify the method of US Patent No. 5,757,264 to assay for PLA2 levels to diagnose ovarian or testicular cancer because the prior art teaches a wide variety of cancer types, all of which demonstrate elevation of PLA2 in serum compared to normal control and thus given the teaching of the prior art, it would be obvious, and one would have been motivated, to diagnose for any and all cancers using the claimed method with a reasonable expectation of success. Further, all of the cancer types tested include carcinomas, as do both ovarian and testicular cancers. Thus it would be expected that at least a subset of ovarian and testicular cancers, carcinomas, could be detected and diagnosed by the method of the combined references.

8. Claims 13-15 are rejected under 35 USC 103 as being unpatentable over US Yamashita et al (Clin. Chim. Acta), of record in view of US Patent No.5,747,264 for the reasons set forth above drawn to the rejection of claims 6-8 and further for the reasons set down herein.

The claims are drawn to a method of monitoring progression, remission, response to therapy of prostate, breast, ovarian or testicular cancer comprising measuring PLA2 levels with an enzyme level cut-off of 4.5 ng/ml in biological fluids wherein an increase in the levels of PLA2 over time is indicative of

progression, a decrease in measured levels of PLA2 over time is indicative of remission or response to therapy.

Yamashita et al teach as previously set forth and further teach a method of monitoring response to therapy in patients with cancers in liver, esophagus, colon, pancreas and stomach by ELISA assay of PLA2 expression in serum two weeks after resection and it was found that all nice patients tested, that is in each of the cancer types tested, there was a reduction in PLA2 levels in the serum (see Figure 3, page 96 and page 97). Yamashita further teach the relationship between serum PLA2 levels and tumor progression and teach specifically that breast cancer patients with T2-T4 or Stage II-IV cancers have significantly higher levels of PLA2 in comparison with T1 or stage I cancers of the same type and that breast cancer patients with lymph node involvement (metastasis) or distant metastasis had significantly higher serum PLA2 than those that did not (see pages 95 and 96 and Figure 3). Yamashita et al teach as previously set forth but do not teach a method of monitoring progression of prostate, ovarian or testicular cancer, remission, response to therapy of prostate, breast, and ovarian cancers or testicular cancer.

US Patent No.5,747,264 teaches as previously set forth.

It would have been *prima facie* obvious and one of ordinary skill in the art would have been motivated to modify the assay of Yamashita et al to monitor the response to therapy in patients with breast and prostate cancers because each of them had been shown to overexpress PLA2 in serum and it would have been *prima facie* obvious and one of ordinary skill in the art would have been motivated to modify the assay of Yamashita et al to monitor the response to therapy in testicular

and ovarian cancers for the reasons set forth above. One would have a reasonable expectation of success in monitoring the response to treatment of these cancer types because just as every single one of the cancer types tested presented with elevated serum PLA2, every single one of the cancer types tested showed a reduction in those levels. Thus it would be expected that the same effect would be seen in all cancer types and individuals overexpressing PLA2 in serum. Further, since remission is by definition a reduction of cancer load and the therapy here is resection which is reduction of tumor load, it would have been obvious to, and one would have been motivated to and would have expected to successfully monitor for remission with the modified method of Yamashita. Finally, it would have been *prima facie* obvious and one of ordinary skill in the art would have been motivated to modify the assay of Yamashita to monitor progression of the claimed cancer types because it is clear that the active cancer is responsible for the overexpression of the PLA2 and since recurrence is a form of progression, it would have been expected that recurrence would present with increased expression of PLA2 in serum and it would be obvious and one would be motivated to and expect to successfully monitor progression by the modified method of Yamashita by assaying for the return of elevated levels of PLA2. In addition, it would have been *prima facie* obvious, and one of ordinary skill in the art would have been motivated assay for progression of breast cancer using the method of the combined references because Yamashita specifically exemplifies and demonstrates the increased level of PLA2 in serum of breast cancer patients with T2-T4 or Stage II-IV cancers which are significantly higher levels of PLA2 in comparison with T1 or stage I cancers of the

same type and that breast cancer patients with lymph node involvement (metastasis) or distant metastasis had significantly higher serum PLA2 than those that did not. Although the combined references does not specifically teach measuring PLA2 levels with an enzyme level cut-off of 4.5 ng/ml for this assay, the claimed method appears to be the same as the prior art method, absent a showing of unobvious differences. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the method of the combined prior art does not possess the same material, structural and functional characteristics of the claimed method. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed method is different from that taught by the combined prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

9. All other objections and rejections recited in Paper No. 3 are withdrawn.

10. No claims allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (703) 305-2181. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached at (703) 308-3995. The fax phone number for this Art Unit is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Effective, February 7, 1998, the Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1642.

Susan Ungar
Primary Patent Examiner
April 26, 2002